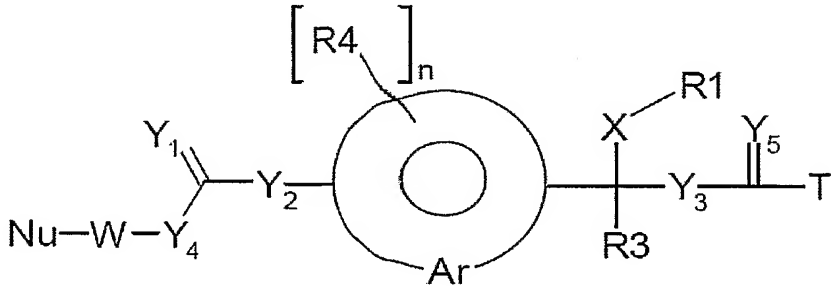
CLAIMS

1. A polymeric cascade prodrug comprising:
   - an amine containing biologically active moiety
   - a masking group having at least one nucleophile and being distinct from the carrier.

2. The prodrug of claim 1 or corresponding polymeric cascade prodrug linker reagent having the following structure:



wherein

T is D or A

D being a residue of an amine containing biologically active moiety and

A being a leaving group;

X is a spacer moiety such as R5-Y_6

Y_1, Y_2 can each be either O, S, or NR6, independently of each other.

Y_3, Y_5 can each be either O or S, independently of each other.

Y_4 is O, NR6, or -C(R7)(R8)-

Y_6 is O, S, NR6, succinimide, maleimide, unsaturated carbon-carbon bonds or any heteratom containing a free electron pair or is absent..

R3 is selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls, cyano, nitro, halogen, carboxy, carboxyalkyl, alkylcarbonyl, or carboxamidoalkyl;

R4 is selected independently from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, substituted or non-substituted linear, branched, or cyclical alkoxy, substituted or non-substituted linear, branched, or cyclical heteroalkyloxy, aryloxy, or heteroaryloxy, cyano, halogen;

R5 is selected from substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls;

R7 and R8 are selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano, or halogen;

R6 is selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls;

R1 is a polymer;

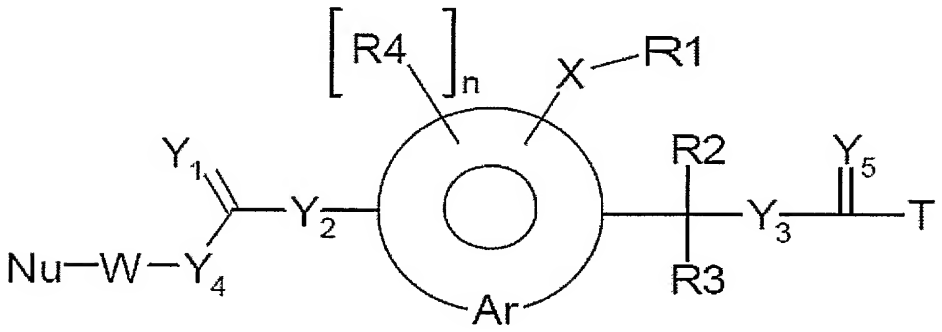
W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl, substituted or nonsubstituted heteroaryls;

Nu is a nucleophile;

n is zero or a positive integer; and

Ar is a multi-substituted aromatic hydrocarbon or a multi-substituted aromatic heterocycle.

3. The prodrug of claim 1 or corresponding polymeric cascade prodrug linker reagent having the following structure:



wherein

T is D or A

D being a residue of an amine containing biologically active molecule and

A being a leaving group;

X is a spacer moiety such as R5-Y_6

Y_1, Y_2 can each be either O, S, or NR6, independently of each other.

Y_3, Y_5 can each be either O or S, independently of each other.

Y_4 is O, NR6, or -C(R7)(R8)-

Y_6 is O, S, NR6, succinimide, maleimide, unsaturated carbon-carbon bonds or any heteratom containing a free electron pair or is absent.

R2 and R3 are selected independently from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-

substituted heteroaryls, cyano, nitro, halogen, carboxy, carboxyalkyl, alkylcarbonyl, or carboxamidoalkyl;
R4 is selected independently from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, substituted or non-substituted linear, branched, or cyclical alkoxy, substituted or non-substituted linear, branched, or cyclical heteroalkyloxy, aryloxy, or heteroaryloxy, cyano, halogen;
R5 is selected from substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls;
R7 and R8 are selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano, or halogen;
R6 is selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls;
R1 is a polymer;
W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl, substituted or nonsubstituted heteroaryls;
Nu is a nucleophile;
n is zero or a positive integer; and
Ar is a multi-substituted aromatic hydrocarbon or a multi-substituted aromatic heterocycle.

4. The prodrug of one of claims 1 to 3, wherein the biologically active moiety is selected from the group of biologically moieties consisting of small molecule biologically active agents or biopolymers.

5. The prodrug of claim 4, wherein the biopolymers are selected from the group of biopolymers consisting of proteins, polypeptides, oligonucleotides and peptide nucleic acids.

6. The prodrug of claim 5, wherein the polypeptides are selected from the group of polypeptides consisting of ACTH, adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin (AAT), alfa-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucagon-like peptides like GLP-1, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza

vaccines, interleukins (1 alfa, 1 beta, 2, 3, 4, 6, 10, 11, 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a, gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, levothyroxine, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), TSH, urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin.

7. The prodrug of claim 5, wherein the protein is a protein prepared by recombinant DNA technology.

8. The prodrug of claim 5, wherein the protein is selected from the group of proteins consisting of antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins.

9. The prodrug of claim 5, wherein the protein is selected from the group of proteins consisting of antibodies, calcitonin, G-CSF, GM-CSF, erythropoietins, hemoglobins, interleukins, insulins, interferons, SOD, somatropin, TNF, TNF-receptor-IgC Fc, glucagon-like peptides like GLP-1,

10. The prodrug of claim 4, wherein the small molecule biologically active agents are selected from the group of agents consisting of central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting, and cardiovascular agents with at least one primary or secondary amino group.

11. The prodrug of claim 4, wherein the small molecule biologically active agents are selected from the group of compounds consisting of daunorubicin, doxorubicin, idarubicin, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxaxin, enoxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamin, dobutamin, lisinopril, serotonin, acivicin and carbutamid.

12. The prodrug of claim 2 or 3, wherein R4 is selected from the group of small substituents consisting of hydrogen, methyl, ethyl, ethoxy, methoxy, and other linear alkyls, cycloalkyls or branched alkyls and heteroalkyl comprising one to six carbon atoms.

13. The prodrug of claim 2 or 3, wherein R1 is selected from the group of polymers consisting of polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES) and other carbohydrate-based polmers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamides) such as poly(hydroxypropylmethacrylamide) (HMPA), poly(acrylates), poly(methacrylates) like poly(hydroxyethylmethacrylate), poly(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid), collagen, gelatin, copolymers, grafted copolymers, cross-linked polymers, and block copolymers from the above listed polymers.

14. The prodrug of claim 2 or 3, wherein R1 is a hydrogel.

15. The prodrug of claim 2 or 3, wherein R1 is a branched or hyperbranched polymer.

16. The prodrug of claim 2 or 3, wherein R1 is a dendrimer or dense star polymer.

17. The prodrug of claim 2 or 3, wherein R1 is a biopolymer.

18. The prodrug of claim 17, wherein R1 is a protein.

19. The prodrug of claim 18, wherein the protein is albumin, an antibody, fibrin, casein or any other plasma protein.

20. The prodrug of any one of claims 2 to 19, wherein R1 further includes one or more biologically active substances.

21. The prodrug of any one of claims 2 to 20, wherein the polymer of R1 has at least one functional group for linkage to X.

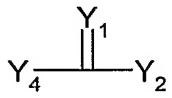
22. The prodrug of claim 21, wherein the at least one functional group is selected from the group of functional groups consisting of carboxylic acid and activated derivatives, amino, maleimide, thiol, sulfonic acid and derivatives, carbonate and derivatives, carbamate and derivatives, hydroxyl , aldehyde, ketone , hydrazine , isocyanate, isothiocyanate, phosphoric acid and derivatives, phosphonic acid and derivatives, haloacetyl, alkyl halides, acryloyl, arylating agents like aryl fluorides, hydroxylamine, disulfides like pyridyl disulfide, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane, and aziridine.

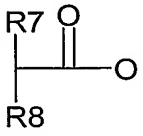
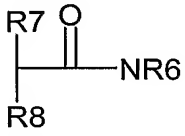
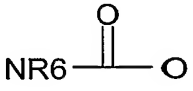
23. The prodrug of claim 21 or 22, wherein the at least one functional group is selected from the group of functional groups consisting of thiol, maleimide, amino, carboxylic acid and derivatives, carbonate and derivatives, carbamate and derivatives, aldehyde, and haloacetyl.

24. The prodrug of one of claims 21 to 23, wherein the bond or group formed between X and R1 is selected from the group of bonds or groups consisting of disulfide, S-succinimido, amide, amino, carboxylic ester, sulphonamide, carbamate, carbonate, there, oxime, hydrazone, urea, thiourea, phosphate, phosphonate.

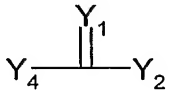
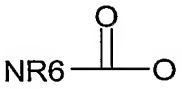
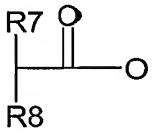
25. The prodrug of any one of claims 21 to 24, wherein the bonds or groups formed between X and R1 is selected from the group of bonds or groups consisting of S-succinimido, amide, carbamate, and urea.

26. The polymeric cascade prodrug linker reagent of any one of claims 2 to 25, wherein A is selected from the group of leaving groups consisting of chloride, bromide, fluoride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy and N-hyroxysulfosuccinimidyl.

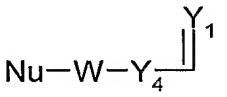
27. The prodrug of claim 2 or 3, wherein the moiety  is preferably selected from the group of moieties consisting of

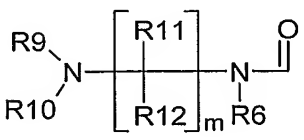
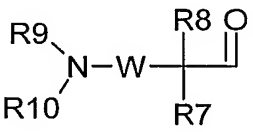
  and 

28. The prodrug of claim 27, wherein the moiety

 is  or 

29. The prodrug of claim 27 or 28 wherein R6 may be a further Nu-W.

30. The prodrug of any one of claims 2 to 29 wherein  is

 or 

m = 2 - 10

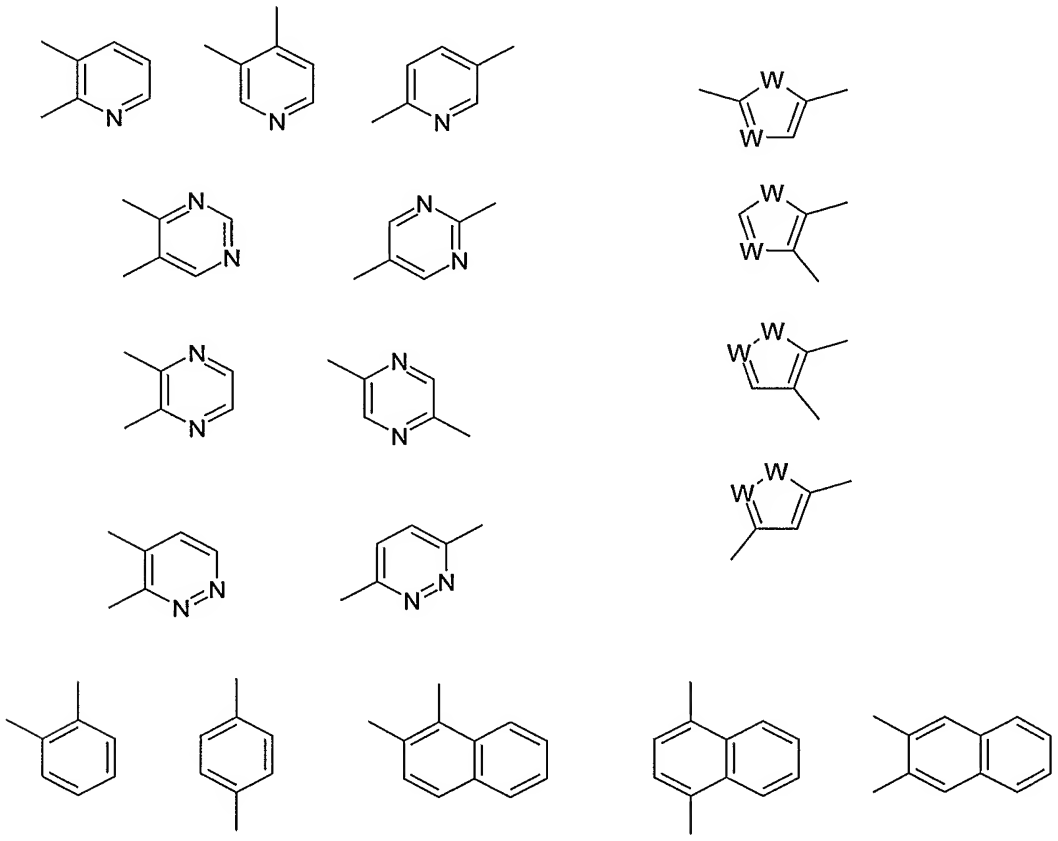
in which R9, R10, R11 and R12 are selected independently from hydrogen, substituted or non-substituted alkyl or heteroalkyl, substituted or non-substituted aryl or heteroaryl.

31. The prodrug of claim 30, wherein R9, 10, R11 and R12 are selected independently from hydrogen or substituted or non-substituted alkyl.

32. The prodrug of any one of claims 2 to 31, wherein Nu is selected from the group of nucleophiles consisting of primary, secondary and tertiary amino groups, thiol, carboxylic acid, hydroxylamine, hydrazine and nitrogen containing heteroaryl.

33. The prodrug of claim 30 or 31, wherein R7 and/or R8 are not hydrogen.

34. The prodrug of claim 2 or 3, wherein Ar is selected from the group of moieties having the following structure:



and wherein W is O, S, or N, independent from each other.

35. The prodrug of claim 2 or 3 wherein Ar is a monocyclic or dicyclic aromatic hydrocarbon or aromatic heterocycle.

36. The prodrug of claim 2 or 3, wherein the Ar is a five-membered or six-membered aromatic hydrocarbon or aromatic heterocycle.

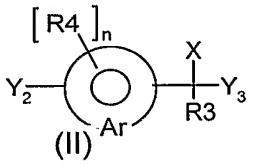
37. The polymeric cascade prodrug linker reagent of any one of the above claims 2-36, in which T is a leaving group A, for covalent conjugation with a biologically active moiety .

38. The polymeric cascade prodrug linker reagent of claim 37, wherein the biologically active moiety is an amine-containing molecule.

39. The polymeric cascade prodrug linker reagent of claim 37 or 38, wherein the biologically active moiety is a peptide, polypeptide or protein.

40. Method for the synthesis of a polymeric prodrug comprising:

- providing a starting molecule of Formula II



(II)

- synthesising at least one intermediate compound from the starting molecule of Formula II; and
- attaching an amine-containing biologically active moiety D to the at least one intermediate compound to form the polymeric prodrug;

wherein

Y_2 is selected from O, S, or NR6

Y_3 is selected from O or S

X is a spacer moiety such as R5-Y_6;

R3 is selected independently from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, cyano, nitro, halogen, carboxy, carboxyalkyl, alkylcarbonyl or carboxamidoalkyl;

R4 is selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, substituted or non-substituted linear, branched, or cyclical alkoxy, substituted or non-substituted linear, branched, or cyclical heteroalkyloxy, aryloxy or heteroaryloxy, cyano, or halogen;

R5 is selected from substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls ;

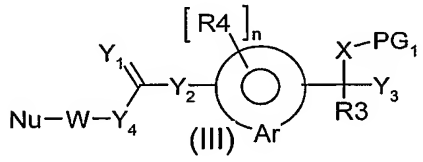
R6 is selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl; and

Y_6 is O, S, NR6, succinimide, maleimide, unsaturated carbon-carbon bonds or a heteratom containing a free electron pair;

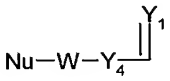
n is zero or a positive integer and

Ar is a multi-substituted aromatic hydrocarbon or a multi-substituted aromatic heterocycle.

41. The method of claim 40, wherein a first one of the at least one intermediate compounds is an intermediate molecule of Formula III



(III)

synthesised by acylating Y_2 with 

and optionally attaching a first protecting group PG_1,

wherein Nu is a nucleophile;

W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl, substituted or nonsubstituted heteroaryls;

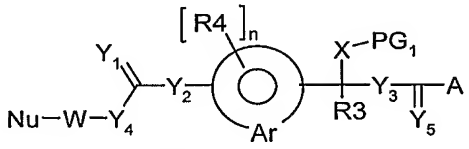
Y_1 is selected from the group of moieties consisting of O, S, or NR6;

Y_4 is selected from the group of moieties consisting of –C(R7)(R8)-, O, or NR6;

R7 and R8 are selected independently from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano or halogen.

R6 is selected selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryls, substituted aryls, substituted or non-substituted heteroaryls;

42. The method of claim 41, wherein a second one of the at least one intermediate compound is an intermediate compound of formula IV



(IV)

formed by activating the compound of Formula III with an activating agent, wherein A is a leaving group and Y_5 is selected from O or S.

43. The method of claim 42, wherein A is selected from chloride, bromide, fluoride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy and N-hydroxysulfosuccinimidyl.

44. The method of one of claims 42 or 43, wherein the activating agent is selected from the group of activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate.

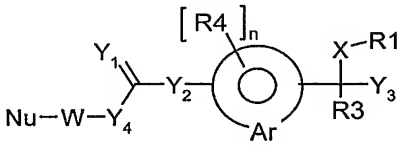
45. The method of one of claims 42 or 43, wherein the amine-containing biologically active moiety D is attached to the second one of the at least one intermediary compound (Formula IV) by displacement of the leaving group A.

46. The method of claim 45 comprising a step of removal of the reversible first protecting group PG_1 from the second one of the at least one intermediate compound.

47. The method of claim 46, wherein the step of removal of the reversible protection group PG_1 is carried out using a reagent selected from the group of reagents consisting of trifluoroacetic acid or DTT.

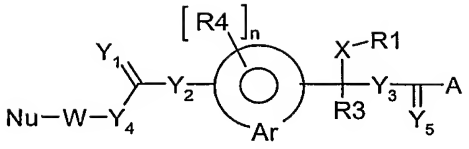
48. The method of any one of claims 46 or 47, further comprising a step of attaching a polymer R1 to X.

49. The method of claim 41, further comprising a step of removing the first polymer protection group PG_1 and attaching a polymer R1 to X to form a third one of the at least one intermediate compound and having a Formula VI.



(VI)

50. The method of claim 49, further comprising a step of activating the third one of the at least one intermediate compound by using an activating agent to form a fourth one of the at least one intermediate compound and having a Formula VII and wherein A is a leaving group.



(VII)

51. The method of claim 50, wherein A is selected from chloride, bromide, fluoride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy and N-hydroxysulfosuccinimidyl.

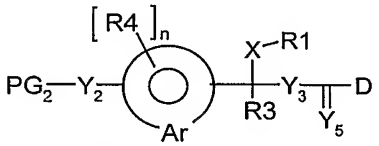
52. The method of claim 50 or 51, wherein the activating agent is selected from the group of activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate.

53. The method of one of claim 50 to 52, wherein the amine-containing biologically active moiety D is attached to the compound of Formula VII by displacement of the leaving group A.

54. The method of claim 40, further comprising a step of reacting the starting molecule of Formula II with a first polymer R1 to attach the first polymer R1 to X.

55. The method of claim 54, further comprising a step of protecting Y_2 with a second protective group PG_2.

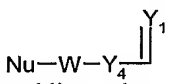
56. The method of claim 54 or 55, further comprising the step of activating the prodrug with an activating agent and reacting with an amine-containing biologically active moiety D to form a fifth one of the at least one intermediate compound and having Formula X



(X)

57. The method of claim 56, wherein the activating agent is selected from the group of activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate

58. The method of claim 56 or 57, wherein the second protecting group PG_2 is removed from Y_2 and Y_2 is acylated with



wherein W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl,

substituted or nonsubstituted heteroaryls ;

Nu is a nucleophile;

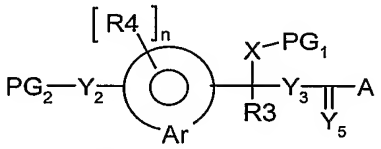
Y_1 is selected from the group of moieties consisting of O, S, or NR6;

Y_4 is selected from the group of moieties consisting of -C(R7)(R8)-, O, NR6; and

R7 and R8 are selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano or halogen.

59. The method of claim 58, wherein the removal of the second reversible group PG_2 is carried out using a reagent selected from the group of reagents consisting of trifluoroacetic acid or DTT.

60. The method of claim 40 comprising a step of attaching a removable first protecting group PG_1 to X and a removable second protecting group PG_2 to the starting compound of Formula II and thereafter activation using an activating agent to form a sixth one of the at least one intermediate compound and having Formula VIII, wherein A is a leaving group



(VIII)

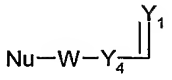
61. The method of claim 60, wherein A is selected from the group of leaving groups selected from the group of leaving groups consisting of chloride, nitrophenoxy, imidazolyly, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentaflourphenoxy and N-hydroxysulfosuccinimidyl.

62. The method of claim 60 or 61, wherein the activating agent is selected from the group of activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate.

63. The method of any one of claims 60 to 62, wherein the amine-containing biologically active moiety D is attached to the sixth one of the at least one intermediate compound by displacement of the leaving group A.

64. The method of claim 63 comprising a step of removing the first protecting group PG_1 from X and attaching a polymer R1.

65. The method of claim 64, wherein the second protecting group PG_2 is removed from Y_2 and Y_2 is acylated with



wherein W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl, substituted or nonsubstituted heteroaryls;

Nu is a nucleophile;

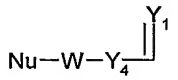
Y1 is selected from the group of moieties consisting of O, S, or NR6;

Y4 is selected from the group of moieties consisting of –C(R7)(R8)-, O, or NR6;

and

R7 and R8 are selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyl or heteroalkyl, aryl, substituted aryl, substituted or non-substituted heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano or halogen.

66. The method of claim 63, wherein the second protecting group PG_2 is removed from Y_2 and Y_2 is acylated with



wherein W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl, substituted or nonsubstituted heteroaryls;

Nu is a nucleophile;

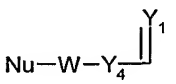
Y1 is selected from the group of moieties consisting of O, S, or NR6;

Y4 is selected from the group of moieties consisting of –C(R7)(R8)-, O, or NR6; ; and

R7 and R8 are selected from hydrogen, substituted or non-substituted linear alkyl, branched alkyl or cyclical alkyl, aryl, substituted aryl, substituted or non-substituted heteroalkyl or heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano or halogen.

67. The method of claim 66 comprising a step of removing the first protecting group PG_1 from X and attaching a polymer R1.

68. The method of claim 54 comprising a step acylating Y_2 with



to form a third one of the at least one intermediate compound;

wherein W is selected from substituted or non-substituted linear, branched or cyclical alkyl, aryls, substituted aryls, substituted or non-substituted linear, branched or cyclical heteroalkyl, substituted or nonsubstituted heteroaryls ;

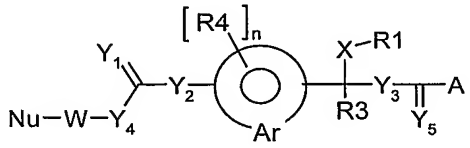
Nu is a nucleophile;

Y_1 is selected from the group of moieties consisting of O, S, or NR6;

Y_4 is selected from the group of moieties consisting of –C(R7) (R8)-, O or NR6; and

R7 and R8 are selected from hydrogen, substituted or non-substituted linear alkyl, branched alkyl or cyclical alkyl, aryl, substituted aryl, substituted or non-substituted heteroalkyl or heteroaryl, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano or halogen.

69. The method of claim 68, further comprising a step of activating the third one of the at least one intermediate compound by using an activating agent to form a seventh one of the at least one intermediate compound and having a Formula VII and wherein A is a leaving group



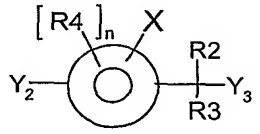
(VII)

70. The method of claim 69, wherein A is selected from the group of leaving groups consisting of chloride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy and N-hyroxysulfosuccinimidyl.

71. The method of claim 69 or 70, wherein the activating agent is selected from the group of activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate.

72. The method of one of claims 69 to 71, wherein the amine-containing biologically active moiety D is attached to the compound of Formula VII by displacement of the leaving group A.

73. The method of any one of claims 40 to 72 wherein the starting molecule of Formula II is replaced by a starting molecule of Formula IIb



IIb

wherein R2 is selected from hydrogen, substituted or non-substituted linear, branched or cyclical alkyls or heteroalkys, aryls, substituted or non-substituted heteroaryls, cyano, nitro, halogen, carboxy, carboxyalkyl, alkylcarbonyl or carboxamidoalkyl.

74. A method for hydrolysing the prodrug of any one of claims 1 to 36 comprising a step of placing the prodrug in solution with a pH of approximately 7.4

75. The method of claim 74, wherein the solution is an extra-cellular fluid.

76. Method of administration of an amine-containing moiety to a living organism comprising:
- a first step of providing a polymeric cascade prodrug according to any one of claims 1 to 39;
- a second step of administering the polymeric cascade prodrug to the living organism; and
- a third step of cleaving the amine-containing moiety from the polymeric cascade prodrug by means of a substantially non-enzymatic reaction.

77. The method of claim 76 , wherein the third step is carried out in an extra-cellular fluid.

78. The method of one of claims 76 or 77, wherein the substantially non-enzymatic reaction comprises a step of hydrolysis.

79. The method of one of claims 76 to 78, wherein the substantially non-enzymatic reaction comprises a step of intramolecular cyclization or intramolecular catalysis.

80. The method of one of claims 76 to 79, further comprising a step of sterically protecting at least part of the linker by a sterically demanding carrier.

81. In an polymeric cascade prodrug according to any one of claims 1 to 39, a method of cleaving the amine-containing moiety from the carrier by a substantially non-enzymatic reaction of the nucleophile-containing linker.

82. The method of claim 81, wherein the substantially non-enzymatic reaction is carried out at a pH of approximately 7.4.

83. The method of claim 81 or 82, wherein the amine-containing moiety attached to the carrier is cleaved in an extra-cellular fluid.

84. The method of one of claims 81 to 83, wherein the substantially non-enzymatic reaction comprises a step of hydrolysis.

85. The method of one of claims 81 to 84, wherein the substantially non-enzymatic reaction comprises a step of intramolecular cyclization or catalysis.

86. The method of one of claims 81 to 85, further comprising a step of sterically protecting at least part of the nucleophile-containing linker by a sterically demanding carrier.

87. The method of any one of claims 81 to 86, wherein the amine-containing moiety is a biologically active moiety.

88. A method of providing a therapeutically useful concentration of a biologically active molecule by *in vivo* cleavage of the biologically active molecule from the prodrug according to any one of claims 1 to 39.